Remarks

Information Disclosure Statement

Applicants filed an Information Disclosure Statement on February 22, 2002, but have not yet received an initialed copy of the PTO-1449 form. A copy of the form is enclosed. Please return an initialed copy of the form with the next Office Action.

The Amendments to the Claims

Claims 14, 19, 20, 29, 53, and 59 have been canceled and reintroduced as claims 81-87, respectively. Claim 61 is amended to incorporate the recitations of canceled claim 69. Claim 70 has been amended to depend from claim 61.

Claim 62 has been amended to recite a fertilized mouse egg. See page 9, lines 12-31 of the specification.

Claim 71 has been amended to recite steps of "introducing a polynucleotide comprising a dominant negative allele of a *PMS2* mismatch repair gene into a fertilized mouse egg, wherein the dominant negative allele comprises a truncation mutation, whereby the fertilized mouse egg becomes hypermutable" and "allowing said fertilized mouse egg to develop into a hypermutable, transgenic mouse." See page 9, lines 21-25 of the specification.

None of the amendments adds new matter.

The Rejection of Claims 14, 19, 20, 29, 53, 58-62, and 69-80 Under 35 U.S.C. § 112, ¶ 1

Claims 14, 19, 20, 29, 53, 58-62, and 69-80 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled for their full scope. Claims 14, 19, 20, 29, 53, and 59 have been canceled and reintroduced as claims 81-87, respectively. Claims 58 and 69 have been canceled. Applicants respectfully traverse the rejection as applied to claims 60-62 and 70-87.

The legal test for whether a disclosure provides adequate enablement for a generic claim is that "the scope of the claims must bear a *reasonable correlation* to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (C.C.P.A. 1970) (emphasis added). To evaluate the scope of enablement the specification provides for the amended claims, the proper standard is whether any experimentation that the skilled worker may need to practice the claimed invention is undue or unreasonable. *In re Wands*, 858 F.2d 731, 736-37, 8 U.S.P.Q.2d (BNA) 1400, 1404 (Fed. Cir. 1988). To make a *prima facie* case of non-enablement using this standard, an Examiner must weigh all the evidence and establish a reasonable basis to question the enablement provided in the specification for the claimed invention. M.P.E.P. §§ 2164.04 and 2164.05, 8th ed., August, 2001.

In the present application, a *prima facie* case of non-enablement of claims 60-62 and 70-87 has not been made. The weight of evidence, including the teachings of the specification and the prior art – and including the references cited in the rejection – favors the conclusion that claims 60-62 and 70-87 are enabled.

The rejected claims are directed to transgenic mice comprising a dominant negative allele of a *PMS2* mismatch repair gene which comprises a truncation mutation and methods of making such mice. The Office Action asserts the specification enables only a transgenic mouse in which

all cells comprise a truncated dominant negative allele of *PMS2* as shown in SEQ ID NO:1 and a method of making such a transgenic mouse by introducing into a fertilized egg a polynucleotide comprising a truncated dominant negative allele of *PMS2* as shown in SEQ ID NO:1. The requirement that the patent holder enable the "full scope" of the claimed invention has never been interpreted to require the enablement of every embodiment within the scope of the claims. *See, e.g., In re Wright*, 999 F.2d 1557, 1563, 27 U.S.P.Q.2d (BNA) 1510, 1515 (Fed. Cir. 1993); M.P.E.P. § 2164.03. Rather, the enablement requirement is satisfied by a disclosure sufficient to teach the skilled artisan how to make and use the invention without undue experimentation. *Wands*, 858 F.2d at 736-37, 8 U.S.P.Q.2d (BNA) at 1404. The specification meets this standard. In fact, the Patent Office has acknowledged that the specification teaches how to make a transgenic mouse with different *PMS2* constructs but asserts that the phenotype of the resultant transgenic mouse would be unpredictable. See Office Action at page 4, lines 6-8.

The U.S. Patent and Trademark Office bears the burden of supplying a reasonable basis for its assertion of unpredictability. The Office Action provides no evidence or reasonable basis to doubt that a mouse expressing a *PMS2* construct other than *hPMS2-134* would have a hypermutable phenotype. On the other hand, Applicants have provided evidence supporting the teaching in the specification that transgenic mice bearing dominant negative alleles of *PMS2* bearing truncation mutations in addition to *hPMS2-134* would have a hypermutable phenotype. The Declaration of Dr. Nicolaides, of record, establishes that expression of a truncated dominant negative allele of *A. thaliana PMS2* in bacterial cells induces hypermutability. The supplemental Declaration of Dr. Kline, of record, further establishes that *in vivo* expression of *hPMS2-134* in transgenic mice induces hypermutability. That truncation mutants of *PMS2* homologs from widely disparate species such as human and plant induce hypermutability in organisms as widely

disparate as mice and bacteria evidences the strong conservation of the mismatch repair pathway among species ranging from bacteria to plants to mammals. Thus, one of skill in the art would have no reason to doubt that transgenic mice bearing truncation mutants of *PMS2* homologs other than *hPMS2-134* would have a hypermutable phenotype.

The specification also provides substantial guidance for identifying truncation mutants of *PMS2* genes that exhibit a dominant negative effect upon mismatch repair. For example, the specification teaches that expression of a dominant negative allele of a mismatch repair gene inhibits mismatch repair activity, thereby causing the cells to accumulate mutations at an abnormally high rate (*i.e.*, the cells become hypermutable). Specification at page 7, lines 1-12. The specification also teaches reliable indicators of the phenotype and assays that permit one of skill in the art to assess mutagenesis. Specification at page 10, lines 15-24. Dr. Kline's supplemental declaration demonstrates that one of skill in the art can readily identify transgenic animals having a hypermutable phenotype because the animals exhibit microsatellite instability, which is a hallmark of hypermutability. Thus, the specification teaches how to make and use hypermutable, transgenic mice comprising a dominant negative allele of a *PMS2* mismatch repair gene which comprises a truncation mutation. No undue experimentation is required.

The Office Action asserts that the specification does not enable the transgenic mouse of claim 60, in which at least 50% of the cells comprise the recited dominant negative allele. It is axiomatic that a specification need not teach that which is known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 223 U.S.P.Q. (BNA) 81, 90 (Fed. Cir. 1986); M.P.E.P. § 2163 II.A.2. The specification teaches that the transgenic animals of the invention can be generated by introducing a dominant negative allele of a *PMS2* mismatch repair gene into embryonic cells by injection or transfection and reintroduction of the cells into the

developing embryo. Specification at page 9, lines 29-31. In addition, methods for generating a transgenic mouse having the transgene in less than all of its cells were well known in the art at the time the present application was filed. For example, U.S. Patent 5,614,396 describes methods for generating transgenic mice by introducing one or more DNA molecules into a precursor pluripotent cell, most preferably an embryonic stem (ES) cell or its equivalent, and culturing the cell *in vivo* to form a transgenic animal. Similarly, U.S. Patent 6,586,655 describes transgenic mice produced by obtaining ES cells from pre-implantation embryos cultured *in vitro*, introducing transgenes into the ES cells and combining the transformed ES cells with blastocysts; the ES cells then colonize the developing embryo. Similarly, US 2002/0038467 teaches that ES cells harboring a transgene aggregate with dissociated mouse embryo cells to form an "aggregation chimera," which can then be implanted into a suitable pseudopregnant female foster animal. Thus, in view of the guidance provided in the specification, the high level of skill in the art, and the state of the art at the time of the invention, it would not have required undue experimentation for the skilled worker to produce the hypermutable transgenic mouse of claim 60.

The Office Action also asserts that the specification does not enable a method of making a hypermutable transgenic mouse by introducing a polynucleotide encoding a dominant negative allele of a *PMS2* mismatch repair gene comprising a truncation mutation into a mouse (claim 61) or a method of growing a mouse comprising a gene of interest and a polynucleotide encoding a dominant negative allele of a *PMS2* mismatch repair gene comprising a truncation mutation (claim 71). To advance prosecution, claims 61 and 71 have been amended to recite a step of introducing the recited dominant negative allele into a fertilized mouse egg.

The U.S. Patent and Trademark Office must weigh the evidence of record as a whole in determining whether claims 60-62 and 70-87 are enabled for their full scope. The Office, however, has not properly weighed the evidence of record. When correctly analyzed, the weight of evidence of record in this application demonstrates that claims 60-62 and 70-87 are enabled.

Applicants respectfully request withdrawal of the rejection.

The Provisional Rejection of Claims 29, 52, 53, and 58-61 Under 35 U.S.C. § 101

Claims 29, 52, 53, and 58-61 stand provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as claims 13-18 and 45-50 of co-pending application Serial No. 09/853,646. Claims 13-18 and 45-50 have been canceled in Serial No. 09/853,646. Thus, there is no longer a basis for a rejection under 35 U.S.C. § 101.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,
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